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## **Sensitive endpoints in extended one-generation reproductive toxicity study versus two generation?**

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Increasing pressure is exerted by some stakeholders to replace the current “golden standard”, two-generation study (OECD TG 416), by an extended one-generation reproductive toxicity study (EOGRTS), because this would considerably reduce the number of animals and other costs involved in these lengthy studies.

Under the new chemicals legislation in Europe, REACH (EU, 2006), two-generation reproductive toxicity study, may be required for substances produced or imported at 100 tonnes per annum or more. At 1000 tonnes per annum, this study becomes a default requirement. The two- generation study receives considerable attention, as it is the only OECD test guideline whereby an organism is exposed during the whole of development, from gamete stage through sexual development.

The one-generation study design from 1983, OECD TG 415, is not a standard information requirement under REACH and is often largely disfavoured because it does not cover the full reproductive cycle, and has not been updated with the developing science. A new study design, EOGRTS, for evaluation of the reproductive toxicity of pesticides and chemicals is currently being evaluated for adoption by OECD and may replace the two-generation reproduction study (OECD 416). The design is based on a paper<sup>1</sup> that incorporates several cohorts of animals to evaluate reproduction, developmental immuno- and neurotoxicity. This guideline will cover more of the reproductive cycle than TG 415 but also include additional evaluations of developmental toxicity. The protocol includes assessment of novel endpoints of concern and developmental landmarks such as anogenital distance, nipple retention (both sensitive endpoints for anti-androgenic effects in male offspring) and mammary gland development (sensitive endpoint for oestrogen action) and may also include assessment of developmental immunotoxicity and neurotoxicity. At the same time it reduces animal use around 40%, and cost and time, the latter being of importance in view of the timelines of REACH. The lack of mating of the offspring appears as a major limitation, because the offspring has been exposed during critical period of development in contrast to the parental generation. Retrospective analysis of available two-generation studies, however, indicate that the assessment included in the study of other endpoints in the male offspring such as histopathology of reproductive organs and semen quality is equally or more sensitive than mating of the male animals. This is currently being debated intensively in the OECD and further retrospective analysis is also ongoing.

The extended one-generation reproductive toxicity study is strongly recommended to replace the current two-generation study since it offers a more extensive evaluation of the F1 generation during development while using less animals overall.

<sup>1</sup>Cooper, R. L., et al (2006). *Crit Rev Toxicol* **36**, 69-98.